APPROVED PROFESSIONAL INFORMATION FOR SERINEM

SCHEDULING STATUS

S3

PROPRIETARY NAMES AND DOSAGE FORM

SERINEM 25 tablets

SERINEM 50 tablets

SERINEM 100 tablets

SERINEM 200 tablets

COMPOSITION

Active ingredient:

Each SERINEM 25 tablet contains 25 mg lamotrigine.

Each SERINEM 50 tablet contains 50 mg lamotrigine.

Each SERINEM 100 tablet contains 100 mg lamotrigine.

Each SERINEM 200 tablet contains 200 mg lamotrigine.

Inactive ingredients:

Lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and sodium starch glycolate.

Contains sugar:

SERINEM 25 contains 12,5 mg lactose monohydrate per tablet.

SERINEM 50 contains 25 mg lactose monohydrate per tablet.

SERINEM 100 contains 50 mg lactose monohydrate per tablet.

SERINEM 200 contains 64,37 mg lactose monohydrate per tablet.

SERINEM 200 also contains FD&C Blue No. 2 as a colourant.

CATEGORY AND CLASS

A 2.5 Anticonvulsants, including antiepileptics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

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.

Pharmacokinetic properties:

Lamotrigine is well and completely absorbed from the gastro-intestinal tract and is metabolised primarily by glucuronidation. The absorption is unaffected by food.

The peak plasma concentration is reached approximately 2,5 hours after an oral dose. The mean elimination half-life is 25 ± 10 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 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 70 hours when co-administered with sodium valproate alone (see **DOSAGE AND DIRECTIONS FOR USE**).

Following multiple administration of lamotrigine (150 mg twice daily) there is modest induction of its own metabolism, resulting in a 25 % decrease in the elimination half-life at steady state.

Lamotrigine is moderately (55 %) bound to plasma proteins.

Clearance adjusted for body weight 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.

Elderly patients:

Population pharmacokinetic analysis including both young and elderly patients with epilepsy, indicated that the clearance of lamotrigine did not change to a clinically relevant extent. After single doses apparent clearance decreased by 12 % from 35 ml/min at age 20 to 31 ml/min at 70 years. The decrease after 48 weeks of treatment was 10 %, from 41 to 37 ml/min between the young and elderly groups. In addition, pharmacokinetics of lamotrigine was studied in 12 healthy elderly individuals 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 with non-elderly adults after single doses of 30 to 450 mg.

Patients with renal impairment:

Patients with chronic renal failure, undergoing haemodialysis and healthy individuals were each given a single 100 mg dose of lamotrigine. Mean clearances 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 individuals. 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 medicine use. Reduced maintenance doses may be effective for patients with significant renal function impairment (see **DOSAGE AND DIRECTIONS FOR USE**).

Patients with hepatic impairment:

A single dose pharmacokinetic study was performed in 24 patients with various degrees of hepatic impairment and 12 healthy individuals as controls. The median apparent clearance of lamotrigine was 0,31; 0,24 or 0,10 ml/min/kg in patients with grade A, B, or C (Child-Pugh classification) hepatic impairment, respectively, compared to 0,34 ml/min/kg in the healthy

individuals. Initial, escalation and maintenance doses should generally be reduced in patients with moderate or severe hepatic impairment (see **DOSAGE AND DIRECTIONS FOR USE**).

INDICATIONS

EPILEPSY:

Adults and children over 12 years:

SERINEM 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:

SERINEM 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:

SERINEM is indicated as add-on treatment for seizures associated with Lennox-Gastaut syndrome.

BIPOLAR DISORDER:

Adults aged 18 years and above:

SERINEM is indicated for the prevention of mood episodes in patients with bipolar disorder who experience predominantly depressive episodes.

CONTRAINDICATIONS

Hypersensitivity to lamotrigine or to any of the inactive ingredients of SERINEM (see **COMPOSITION**).

WARNINGS AND SPECIAL PRECAUTIONS

Clinical worsening and suicide risk:

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic medicines such as SERINEM in several indications. Patients should therefore be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) are to 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 medicines for bipolar disorder. Patients receiving SERINEM for bipolar disorder should therefore 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.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing SERINEM, in patients who experience these symptoms, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Severe convulsive seizures including status epilepticus may lead to rhabdomyolysis, multi-organ dysfunction and disseminated intravascular coagulation, usually with fatal outcome. Similar cases have occurred in association with the use of SERINEM.

Patients receiving SERINEM should be closely monitored (including changes in hepatic, renal and clotting parameters).

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 SERINEM. 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 SERINEM may provoke rebound seizures. The risk may be reduced by tapering off the withdrawal of SERINEM over a period of two weeks.

The body weight of a child must be monitored and the dose reviewed as changes in body weight occur. If the dose calculated for children, according to body weight, does not equate to whole tablets, the dose to be used 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 SERINEM. Although the majority of rashes usually resolve when SERINEM is discontinued, irreversible scarring and cases of associated death have been reported. A mild rash may subside even with continuation of SERINEM therapy, however close monitoring is essential. Serious and potentially life-threatening skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported especially in children and in patients using valproate (see **SIDE EFFECTS**). 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; healthcare 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 SERINEM and exceeding the recommended dose escalation of SERINEM (see **DOSAGE AND DIRECTIONS FOR USE**).
- Concomitant use of valproate, which increases the mean half-life of SERINEM nearly two-fold (see **DOSAGE AND DIRECTIONS FOR USE**).

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 SERINEM withdrawn immediately unless the rash is clearly not medicine-related.

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 and liver, thrombocytopenia and aseptic meningitis. The syndrome shows a wide spectrum of clinical severity and may lead to disseminated intravascular coagulation and multi-organ 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 SERINEM therapy discontinued if an alternative aetiology cannot be immediately established.

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

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

Effects on ability to drive and use machines:

SERINEM may cause dizziness and diplopia. Caution is therefore advised before driving a vehicle or operating machinery until the effects of SERINEM are known.

Lactose warning:

SERINEM contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions of galactose intolerance, e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take SERINEM.

INTERACTIONS

Uridine 5'-diphospho-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes, and interactions between lamotrigine and medicines metabolised by cytochrome P450 enzymes are unlikely to occur. Lamotrigine may induce its own metabolism, but the effect is modest and unlikely to have significant clinical consequences.

Effects of other medicines on glucuronidation of lamotrigine:

Medicines that significantly inhibit glucuronidation of lamotrigine (doubling of lamotrigine half-life)	**Medicines that significantly induce glucuronidation of lamotrigine (halving lamotrigine half-life)**
Valproate	Carbamazepine Phenytoin Primidone Phenobarbital Rifampicin Ethinyloestradiol/levonorgestrel combination*

*Other oral contraceptive and HRT treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters.

Interactions involving antiepileptic medicines:

(See **DOSAGE AND DIRECTIONS FOR USE**.)

Valproate, which inhibits the glucuronidation of lamotrigine,
significantly reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold.
Certain antiepileptic medicines (such as phenytoin, carbamazepine, phenobarbital and primidone) which induce hepatic drug-
metabolising enzymes, induce the glucuronidation of lamotrigine and significantly enhance the metabolism of lamotrigine, leading to a halving of the elimination half-life of SERINEM.
There have been reports of central nervous system events including nausea, blurred vision, dizziness, diplopia and ataxia in patients taking carbamazepine following the introduction of SERINEM. These reactions usually resolve when the dose of carbamazepine is reduced.

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

Interactions involving other psychotropic medicines:

The pharmacokinetics of lithium were not altered by co-administration of 100 mg SERINEM per day.
Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine, and caused only a slight increase in the AUC of lamotrigine glucuronide.
In vitro experiments indicated that the formation of 2-*N*-glucuronide (the primary metabolite of lamotrigine) was minimally inhibited by co-incubation with amitriptyline, bupropion, clonazepam,

haloperidol or lorazepam. Bufuralol metabolism data from human liver microsome suggested that lamotrigine does not reduce the clearance of medicines metabolised predominantly by CYP2D6. Results of *in vitro* experiments also suggest that clearance of lamotrigine is unlikely to be affected by clozapine, phenelzine, risperidone, sertraline or trazodone.

Interactions involving hormonal contraceptives:

Effect of hormonal contraceptives on lamotrigine pharmacokinetics:

Serum lamotrigine concentrations gradually increased during the course of the week of inactive medication (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during co-therapy. Breakthrough seizures have been reported in women using contraceptives.

Effect of lamotrigine on hormonal contraceptive pharmacokinetics:

Co-administration of 300 mg had no effect on the pharmacokinetics of the ethinyloestradiol component of a combined oral contraceptive pill. A modest increase in oral clearance of the levonorgestrel component was observed, resulting in an AUC and C_{max} reduction in levonorgestrel. Measurement of serum follicle-stimulating hormone (FSH), luteinising hormone (LH) and oestradiol 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. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see **WARNINGS AND SPECIAL PRECAUTIONS**). 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. Cases of unplanned pregnancy, menstrual disorders and amenorrhoea have been reported. Any change in the menstrual bleeding patterns should be reported to the healthcare practitioner.

Interactions involving other medicines:

It was 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 appropriate treatment regimen should be used (see **DOSAGE AND DIRECTIONS FOR USE**).

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 **DOSAGE AND DIRECTIONS FOR USE**).

Atazanavir/ritonavir (300 mg/100 mg) administered for 9 days reduced the plasma AUC and C_{max} of SERINEM (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 **DOSAGE AND DIRECTIONS FOR USE**).

In vitro assessments demonstrate that SERINEM, but not the 2-*N*-glucuronide metabolite, is an inhibitor of organic cation transporter 2 (OCT2) at potentially clinically relevant concentrations. These data demonstrate that SERINEM is an inhibitor of OCT2, with an IC_{50} value of 53,8 µM. Co-administration of SERINEM with renally excreted medicines, which are substrates of OCT2 (e.g. metformin, gabapentin and varenicline), may result in increased plasma levels of these medicines.

Using a chronic, high dose of paracetamol may reduce the half-life and AUC of lamotrigine.

HUMAN REPRODUCTION:

The safety of SERINEM in pregnancy and lactation has not been established.

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

antiepileptic 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 antiepileptic medicines could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics.

Pregnancy:

SERINEM has a slight inhibitory effect on dihydrofolic acid reductase and could therefore theoretically lead to an increased risk of embryofetal damage by reducing folic acid levels. Intake of folic acid when planning pregnancy and during early pregnancy may be considered. Physiological changes during pregnancy may affect SERINEM levels and/or therapeutic effect. There have been reports of decreased SERINEM plasma levels during pregnancy with a potential risk of loss of seizure control. After birth SERINEM levels may increase rapidly with a risk of dose-related adverse events. Therefore, SERINEM serum concentrations should be monitored before, during and after pregnancy, as well as shortly after birth. If necessary, the dose should be adapted to maintain the SERINEM serum concentration at the same level as before pregnancy or adapted according to clinical response. In addition, dose-related undesirable effects should be monitored after birth.

Lactation:

SERINEM has been reported to pass into breast milk in highly variable concentrations, resulting in total SERINEM levels in infants of up to approximately 50 % of the mother's. Therefore, in some breastfed infants, serum concentrations of SERINEM may reach levels at which pharmacological effects occur. However, no adverse effects were observed in some infants. Should a woman decide to breastfeed while on therapy with SERINEM, the infant should be monitored for adverse effects.

DOSAGE AND DIRECTIONS FOR USE

It is important to adhere to the recommended dosages especially in combination therapy with valproate where one-tenth to one-fifth of the normal SERINEM dose is used.

Do not exceed the maximum dosage (see **WARNINGS AND SPECIAL PRECAUTIONS**).

General dosing recommendations:

Administration:

Prescribers should assess the need for escalation to maintenance dose when restarting SERINEM in patients who have discontinued SERINEM for any reason, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for SERINEM (see **WARNINGS AND SPECIAL PRECAUTIONS**). The greater the interval of time since the previous dose, the more consideration should be given to escalation to the maintenance dose. When the interval since discontinuing lamotrigine exceeds five half-lives (see **Pharmacokinetic properties**), SERINEM should generally be escalated to the maintenance dose according to the appropriate schedule. It is recommended that SERINEM not be restarted in patients who have discontinued due to rash associated with prior treatment with SERINEM.

EPILEPSY:

When concomitant antiepileptic medicines are withdrawn to achieve SERINEM monotherapy or other antiepileptic medicines are added on to treatment regimens containing SERINEM, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see **INTERACTIONS**).

To ensure a therapeutic dose is maintained the body weight of a child must be monitored, and the dose reviewed as weight changes occur. If a calculated dose of SERINEM (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: 25 mg once daily for two weeks, followed by 50 mg once daily for two weeks. The dosage may be increased by a maximum of 50 mg to 100 mg every 1 to 2 weeks until the optimal response is achieved.

Maintenance dose in monotherapy: The usual dose to achieve optimal response is 100 mg to 200 mg per day given in one dose or two divided doses. Some patients have required 500 mg per day of SERINEM 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 or other medicines (see **INTERACTIONS**) that induce lamotrigine glucuronidation with/without other antiepileptic medicines (except valproate), the initial SERINEM 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 to 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200 mg to 400 mg per day given in two divided doses.

In those patients taking sodium valproate with/without any other antiepileptic medicine, the initial SERINEM 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 mg to 50 mg every 1 to 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 mg to 200 mg per day given once a day or in two divided doses.

In those patients taking oxcarbazepine 1 200 mg per day, without any other inducers or inhibitors of lamotrigine glucuronidation, the initial SERINEM dose 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 – 100 mg every 1 to 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 mg to

200 mg per day given once a day or in two divided doses.

Recommended treatment regimen for adults > 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 other concomitant medicine		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, phenobarbital, primidone, or with other inducers of lamotrigine glucuronidation (see **INTER-ACTIONS**)	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.
	With	25 mg	50 mg (once a	100 – 200 mg

	oxcarbazepine without inducers or inhibitors of lamotrigine glucuronidation	(once a day)	day)	(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 is currently not known (see **INTERACTIONS**), the treatment regimen as recommended for SERINEM 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 **WARNINGS AND SPECIAL PRECAUTIONS**).

Children aged 2 to 12 years:

To ensure a therapeutic dose is maintained the body weight of a child must be monitored and the dose reviewed as changes in body weight occur. If the doses calculated for children, according to body weight, 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 antiepileptic medicines or other medicines (see **INTERACTIONS**) that induce lamotrigine glucuronidation with/without other antiepileptic medicines (except valproate), the initial SERINEM is 0,6 mg/kg body weight per day given in 2 divided doses for two weeks, followed by 1,2 mg/kg per day for 2 weeks. Thereafter, the dose should be increased by a maximum of 1,2 mg/kg every 1 to 2 weeks until optimal response is achieved. The usual maintenance dose to achieve optimal response is 5 – 15 mg/kg per day given in 2 divided doses. A maximum daily dose of 400 mg must not be exceeded.

In children taking sodium valproate with or without any other antiepileptic medicine, the initial SERINEM dose is 0,15 mg/kg body weight per day given once a day for two weeks, followed by 0,3 mg/kg body weight per 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 per day given once a day 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 SERINEM dose is 0,3 mg/kg body weight per day given once a day or in 2 divided doses for 2 weeks, followed by 0,6 mg/kg per day given once a day or in 2 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 per day given once a day or in 2 divided doses, with a maximum of 200 mg/day.

Recommended treatment regimen for children aged 2 – 12 years (total daily dose in mg/kg body weight per day)

Treatment regimen		**Weeks 1 + 2**	**Weeks 3 + 4**	**Maintenance dose**
Add-on therapy with valproate regardless of any concomitant medicine		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 2 divided doses) to a maximum of 200 mg/day.
Add-on therapy without valproate	This dosage regimen should be used with: phenytoin, carbamazepine, phenobarbital, primidone, or with other inducers of lamotrigine	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 2 divided doses) to a maximum of 400 mg/day.

	glucuronidation (see **INTERACTIONS**)			
	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 2 divided doses) to a maximum of 200 mg/day.
In patients taking antiepileptic medicines where the pharmacokinetic interaction with lamotrigine is currently not known (see **INTERACTIONS**), the treatment regimen as recommended for SERINEM with concurrent valproate should be used.				
*If the calculated daily dose in patients taking valproate is 1 – 2 mg, then 2 mg SERINEM may be taken on alternate days for the first 2 weeks. If the calculated daily dose is less than 1 mg, then SERINEM should not be used.				

The recommended initial dose and subsequent dose escalation should not be exceeded, to minimise the risk of skin rash (see **WARNINGS AND SPECIAL PRECAUTIONS**).
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 to 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 SERINEM 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 **WARNINGS AND SPECIAL PRECAUTIONS**).

SERINEM 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 SERINEM to a maintenance stabilisation dose over 6 weeks (see table below) after which other psychotropic and/or antiepileptic medicines can be withdrawn.

Adjunctive therapy should be considered for the prevention of manic episodes, as efficacy with SERINEM 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 with 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 2 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 phenobarbital 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 SERINEM e.g. lithium, bupropion OR monotherapy with SERINEM	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)
In patients taking antiepileptic medicines where the pharmacokinetic interaction with SERINEM is currently not known, the dose escalation as recommended for SERINEM 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 inhibitors such as valproate concomitantly, the initial dose of SERINEM 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. To achieve optimal response, the usual target dose is 100 mg/day given once a day or in two divided doses. Depending on the clinical response, the dose may be increased to a maximum daily dose of 200 mg.

b) Adjunct therapy with enzyme inducers e.g. carbamazepine and phenobarbital in patients NOT taking valproate:

In patients taking enzyme inducers such as carbamazepine and phenobarbital (see **INTERACTIONS**) and NOT taking valproate, the initial dose of SERINEM is 50 mg once a day for 2 weeks, followed by 100 mg/day in two divided doses for 2 weeks. The dose is to 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 to achieve optimal response, the usual target dose 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 SERINEM e.g. lithium, bupropion, OR monotherapy with SERINEM:

The initial dose of SERINEM in patients taking concomitant medicines with no known/theoretical pharmacokinetic interaction with lamotrigine or in monotherapy, is 25 mg once daily for 2 weeks, followed by 50 mg once a day (or in two divided doses) for 2 weeks. The dose is to be increased to 100 mg/day in week 5. To achieve optimal response, the usual target dose is 200 mg/day given once a day or in two divided doses, however doses ranging from 100 – 400 mg have been used.

Maintenance stabilisation total daily dose in bipolar disorder following the withdrawal of concomitant psychotropic or antiepileptic medicines:

Once the target daily maintenance stabilisation dose has been achieved, other psychotropic medicines may be withdrawn as shown below:

<table>
<tr><th>Treatment regimen</th><th>Week 1</th><th>Week 2</th><th>Week 3 onwards*</th></tr>
<tr><td>a) Following withdrawal of enzyme inhibitors e.g. valproate</td><td>Double the stabilisation dose, not exceeding 100 mg/week
i.e. 100 mg/day target stabilisation dose will be increased in week 1 to 200 mg/day</td><td colspan="2">Maintain this dose (200 mg/day)
(two divided doses)</td></tr>
<tr><td rowspan="3">b) Following withdrawal of enzyme inducers e.g. carbamazepine depending on</td><td>400 mg</td><td>300 mg</td><td>200 mg</td></tr>
<tr><td>300 mg</td><td>225 mg</td><td>150 mg</td></tr>
<tr><td>200 mg</td><td>150 mg</td><td>100 mg</td></tr>
</table>

original dose			
c) Following withdrawal of other psychotropic or antiepileptic medicines with no known clinical pharmaco-kinetic interaction with SERINEM e.g. lithium, bupropion	Maintain target dose achieved in dose escalation (200 mg/day) (two divided doses) (range of 100 – 400 mg)		
In patients taking psychotropic or antiepileptic medicines where the pharmacokinetic interaction with SERINEM is currently not known, the treatment regimen as recommended for SERINEM 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:

Once valproate, an enzyme inducer, has been discontinued, the dose of SERINEM should be increased to double the original target stabilisation dose. This adjusted dose is to be maintained.

b) Following withdrawal of adjunct therapy with enzyme inducers e.g. carbamazepine, depending on original maintenance dose:

The dose of SERINEM should be gradually reduced over a 3 week period as the inducer is withdrawn.

c) Following the withdrawal of adjunct therapy with other psychotropic or antiepileptic medicines with no known pharmacokinetic interaction with SERINEM e.g. lithium,

bupropion:

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

Adjustments of SERINEM daily dosing in patients with bipolar disorder following addition of other medicine:

There is no clinical experience in adjusting the SERINEM daily dose following the addition of other medicines.

However, based on medication interaction studies, the following recommendations have been made (see table below):

Adjustments of SERINEM daily dosing in patients with bipolar disorder following the addition of other medicine:

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 SERINEM	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	200 mg	200 mg	300 mg	400 mg
	150 mg	150 mg	225 mg	300 mg

in patients NOT taking valproate and depending on the original dose of SERINEM	100 mg	100 mg	150 mg	200 mg
c) Addition of other psychotropic or antiepileptic medicines with no known clinical pharmacokinetic interaction with SERINEM e.g. lithium, bupropion	Maintain target dose achieved in dose escalation (200 mg/day) (range 100 – 400 mg)			
In patients taking psychotropic or antiepileptic medicines where the pharmacokinetic interaction with SERINEM is currently not known, the treatment regimen as recommended for SERINEM with concurrent valproate should be used.				

Discontinuation of SERINEM in patients with bipolar disorder:

No increase in the incidence, severity or type of adverse reactions following abrupt termination of lamotrigine versus placebo has been reported. Therefore, patients may terminate SERINEM without a step-wise reduction of dose.

Children (less than 18 years of age):

Safety and efficacy of SERINEM in bipolar disorder have not been evaluated in this age group. Therefore, a dosage recommendation cannot be made.

General dosing recommendations for SERINEM in special patient populations:

Women taking hormonal contraceptives:

a) Starting SERINEM in patients already taking hormonal contraceptives:

Although an oral contraceptive has been shown to increase the clearance of lamotrigine (see **WARNINGS AND SPECIAL PRECAUTIONS** and **INTERACTIONS**), no adjustments to the recommended dose escalation guidelines for SERINEM should be necessary solely based on the use of hormonal contraceptives. Dose escalation should follow the recommended guidelines based on whether SERINEM is added to an inhibitor of lamotrigine glucuronidation e.g. valproate, whether SERINEM is added to an inducer of lamotrigine glucuronidation e.g. carbamazepine, phenytoin, phenobarbital, primidone or rifampin, or whether SERINEM is added in the absence of valproate, carbamazepine, phenytoin, phenobarbital, primidone or rifampicin (see table: **Recommended treatment regimen for adults over 12 years of age**).

b) Starting hormonal contraceptives in patients already taking maintenance doses of SERINEM and not taking inducers of lamotrigine glucuronidation:

The maintenance dose of SERINEM will in most cases need to be increased by as much as two-fold according to the individual clinical response (see **WARNINGS AND SPECIAL PRECAUTIONS** and **INTERACTIONS**).

c) Stopping hormonal contraceptives in patients already taking maintenance doses of SERINEM and not taking inducers of lamotrigine glucuronidation:

The maintenance dose of SERINEM will in most cases need to be decreased by as much as 50 % according to the individual clinical response (see **WARNINGS AND SPECIAL PRECAUTIONS** and **INTERACTIONS**).

Use with atazanavir/ritonavir:

No adjustments to the recommended dose escalation of SERINEM should be necessary when added to the existing atazanavir/ritonavir therapy.

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

decreased if atazanavir/ritonavir is discontinued. SERINEM monitoring in plasma should be conducted before and during 2 weeks after starting or stopping atazanavir/ritonavir, in order to see if SERINEM dose adjustment is needed (see **INTERACTIONS**).

Use with lopinavir/ritonavir:

No adjustments to the recommended dose escalation of SERINEM should be necessary when SERINEM is added to the existing lopinavir/ritonavir therapy.

In patients already taking maintenance doses of SERINEM and not taking glucuronidation inducers, the SERINEM dose may need to be increased if lopinavir/ritonavir is added or decreased if lopinavir/ritonavir is discontinued. SERINEM monitoring in plasma should be conducted before and during 2 weeks after starting or stopping lopinavir/ritonavir, in order to see if SERINEM dose adjustment is needed (see **INTERACTIONS**).

Elderly patients (above 65 years):

No dosage adjustment from the recommended schedule is required. The pharmacokinetics of SERINEM 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 SERINEM to patients with renal failure. For patients with end-stage renal failure, initial doses of SERINEM should be based on patients' antiepileptic medicines regimen: reduced maintenance doses should be used for patients with significant renal functional impairment.

SIDE EFFECTS

EPILEPSY:

Infections and infestations:

Less frequent: infection

Blood and lymphatic system disorders:

Less frequent: haematological abnormalities including anaemia, neutropenia, leucopenia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis

Frequency unknown: disseminated intravascular coagulation, red cell aplasia

Haematological abnormalities may or may not be associated with a hypersensitivity syndrome (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Immune system disorders:

Less frequent: hypersensitivity syndrome*, angioedema

Frequency unknown: progressive immunosuppression

*Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms, including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multi-organ failure. 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 SERINEM discontinued if an alternative aetiology cannot be established (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Psychiatric disorders:

Frequent: irritability

Less frequent: aggression, tics, hallucinations, confusion, anxiety, depression, amnesia

Nervous system disorders:

Frequent: headache, drowsiness, insomnia, dizziness, tremor, paraesthesia, nystagmus, poor coordination

Less frequent: ataxia, agitation, unsteadiness, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency, dysarthria

SERINEM may worsen parkinsonian symptoms in patients with pre-existing Parkinson's disease and there were isolated reports of extrapyramidal effects and choreoathetosis in patients without this underlying condition.

Eye disorders:

Frequent: diplopia, blurred vision

Less frequent: conjunctivitis

Ear and labyrinth disorders:

Frequent: vertigo

Cardiac disorders:

Less frequent: chest pain

Vascular disorders:

Frequency unknown: vasculitis

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: apnoea, rhinitis

Gastrointestinal disorders:

Frequent: nausea, gastrointestinal disturbance, vomiting, diarrhoea

Less frequent: constipation, dry mouth, dyspepsia

Frequency unknown: oesophagitis, pancreatitis

Hepato-biliary disorders:

Less frequent: increased liver function tests, hepatic dysfunction, hepatic failure

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

Musculoskeletal, connective tissue and bone disorders:

Less frequent: lupus-like reactions

Frequency unknown: rhabdomyolysis

General disorders and administration site conditions:

Frequent: tiredness

Less frequent: asthenia

Frequency unknown: multi-organ failure.

BIPOLAR DISORDER:

The side effects below should be considered alongside those seen in epilepsy for an overall safety profile of SERINEM.

Nervous system disorders:

Frequent: headache, agitation, somnolence, dizziness

Skin and subcutaneous tissue disorders:

Frequent: skin rash

Less frequent: Stevens-Johnson syndrome, erythema multiforme, petechia

Musculoskeletal, connective tissue and bone disorders:

Frequent: arthralgia, back pain

General disorders and administration site conditions:

Frequent: pain

Less frequent: fever.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms:

Overdose has resulted in symptoms including drowsiness, nausea, vomiting, nystagmus, ataxia, dry mouth, impaired consciousness and coma.

Treatment:

There is no known antidote to lamotrigine overdose.

Treatment is supportive and symptomatic.

IDENTIFICATION

SERINEM 25: White, round, flat faced, bevel edged tablets plain on both sides, with a diameter of 6,0 mm and a thickness of 2,2 mm.

SERINEM 50: White, round shaped, biconvex tablets plain on both sides, with a diameter of 7,0 mm and a thickness of 3,9 mm.

SERINEM 100: White, round shaped, biconvex tablets plain on both sides, with a diameter of 9,0 mm and a thickness of 5,2 mm.

SERINEM 200: Light blue coloured, round shaped, biconvex tablets plain on both sides, with a diameter of 11,0 mm and a thickness of 5,2 mm.

PRESENTATION

Transparent PVC/PVDC/silver aluminium foil blister strips, containing 10 tablets each.

6 blister strips are packed in an outer carton.

STORAGE INSTRUCTIONS

Store at or below 25 °C, in a dry place.

Keep blister strips in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

SERINEM 25: 46/2.5/0412

SERINEM 50: 46/2.5/0413

SERINEM 100: 46/2.5/0414

SERINEM 200: 46/2.5/0415

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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Cape Town, 8001

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