APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

PROPRIETARY NAME (AND DOSAGE FORM):

ZESITON 5 mg TABLETS (Dispersible tablet)

ZESITON 25 mg TABLETS (Dispersible tablet)

ZESITON 50 mg TABLETS (Dispersible tablet)

ZESITON 100 mg TABLETS (Dispersible tablet)

ZESITON 200 mg TABLETS (Dispersible tablet)

COMPOSITION:

ZESITON5 mg TABLETS: Each uncoated tablet contains lamotrigine 5 mg.

ZESITON 25 mg TABLETS: Each uncoated tablet contains lamotrigine 25 mg.

ZESITON 50 mg TABLETS: Each uncoated tablet contains lamotrigine 50 mg.

ZESITON 100 mg TABLETS: Each uncoated tablet contains lamotrigine 100 mg.

ZESITON 200 mg TABLETS: Each uncoated tablet contains lamotrigine 200 mg.

Contains sucralose.

The other ingredients are black currant flavour; cellulose, microcrystalline; magnesium carbonate; magnesium stearate; polacrilin potassium, povidone and sucralose.

PHARMACOLOGICAL CLASSIFICATION:

A.2.5 Antiepileptics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Lamotrigine is a phenyltriazine derivative.

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 gut. The absorption is unaffected by food.

The time to peak concentration is 1,4 to 4,8 hours. 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 59 hours when co-administered with valproic acid alone (see **"Interactions" and "Dosage and Directions for Use"**).
Following multiple dose 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.
Hepatic metabolism followed by renal excretion is the principal route of elimination of lamotrigine**.**
Clearance adjusted for bodyweight is higher in children aged 12 years and under than in adults, with the highest values in children less than 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.

Special populations

Elderly:

Results of a population pharmacokinetic analysis including both young and elderly patients with epilepsy, enrolled in the same trials, indicated that the clearance of lamotrigine did not change to a clinical relevant extent. After single doses, apparent clearance decreased by 12 % from 35 ml/min at age 20 to 31 ml/min at 70 years. The decrease after 48 weeks of treatment was 10 % from 41 to 37 ml/min between the young and elderly groups. In addition, pharmacokinetics of lamotrigine was studied in 12 healthy elderly subjects

following a 150 mg single dose. The mean clearance in the elderly (0,39 ml/min/kg) lies within the range of the mean clearance values (0,31 to 0,65 ml/min/kg) obtained in 9 studies with non-elderly adults after single dose of 30 to 450 mg.

Patients with renal impairment:

Twelve volunteers with chronic renal failure, and another 6 individuals undergoing haemodialysis were given a single 100 mg dose of lamotrigine. Mean CL/F were 0, 42 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, 8 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 dose of lamotrigine should be based in patients antiepileptic drug (AED) regimen; reduced maintenance doses should be used in patients with significant renal functional impairment (see **" Dosage and Directions For Use").**

Patients with hepatic impairment:

A single-dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as control. The median apparent clearance of lamotrigine was 0,31, 0,24 and 0,10 ml/min/kg in patients with grade A, B or C (Child-Plough Classification) Hepatic impairment, respectively, compared to 0,34 ml/min/kg in healthy controls. Reduced doses should be used in patients with grade B or C hepatic impairment (see **"Dosage and Directions For Use").**

INDICATIONS:

EPILEPSY: ***Adults and children over 12 years***

ZESITON are 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

ZESITON are 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.

Lennox-Gastaut Syndrome

ZESITON are indicated as add-on treatment for seizures associated with Lennox-Gastaut Syndrome.

BIPOLAR DISORDER: ***Adults 18 years of age and over***

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

CONTRA-INDICATIONS:

ZESITON are contra-indicated in the following circumstances:

- Individuals with known hypersensitivity to lamotrigine or any of the ingredients of **ZESITON**.
- The safety of **ZESITON** in pregnancy and lactation has not been established.
- Renal and hepatic function impairment. The use of **ZESITON** in patients with impairment of hepatic or renal function is contra-indicated.
- Patients over the age of 65 years.

WARNINGS AND SPECIAL PRECAUTIONS:

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 **ZESITON**.

Patients receiving **ZESITON** should be closely monitored for 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 **ZESITON**. 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 **ZESITON** may provoke rebound seizures. The risk may be reduced by tapering off the withdrawal of **ZESITON** 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 **ZESITON**. Although the majority of rashes usually resolve when **ZESITON** are discontinued, irreversible scarring and cases of associated death have been reported, close monitoring is essential. Less frequently, 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 concomitantly (see **"Side-Effects"**). Cases have also been reported after prolonged treatment (6 months).

The estimated incidence of serious skin rashes in adults is 1 in 1000. 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; doctors 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 **ZESITON** and exceeding the recommended dose escalation of **ZESITON** (see **"Dosage and Directions For Use"**).
- Concomitant use of valproate, which increases the mean half-life of **ZESITON** 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 **ZESITON** 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 and thrombocytopenia. The syndrome shows a wide spectrum of clinical severity and may lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (e.g. fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present the patient should be evaluated immediately and **ZESITON** therapy discontinued if an alternative aetiology cannot be immediately established.

Bipolar Disorder: The possibility of a suicide attempt is inherent in bipolar disorder, and close supervision of high-risk patients should accompany medicine therapy.

ZESITON inhibits dihydrofolate reductase and should be used with caution with other folate antagonists.

Effects on the ability to drive and use machines:

ZESITON may cause dizziness, drowsiness and blurred or double vision. Driving and operating machinery should be avoided until the effect of **ZESITON** on the individual patient is determined.

INTERACTIONS:

Enzyme-inducing medicines (such as phenytoin, carbamazepine, phenobarbitone and primidone) enhance the metabolism of **ZESITON** leading to an increased clearance and subsequent reduction of the elimination half-life of **ZESITON**. Concomitant use of valproic acid increases the half-life and plasma concentrations of **ZESITON** due to competition for hepatic glucuronidation. Plasma concentrations of valproic acid may decrease slightly when **ZESITON** is added (see "**Pharmacokinetic properties"**).

Evidence to date has not shown that **ZESITON** affects the plasma concentration of other concomitant antiepileptic medicines. **ZESITON** does not displace other antiepileptic medicines from protein binding sites.

Use with rifampicin significantly increased the clearance of lamotrigine. The total urinary excretion of lamotrigine and the amount excreted as glucuronide were significantly higher compared with placebo.

A study in healthy subjects found that ritonavir boosted lopinavir decreased the steady-state minimum plasma concentration of lamotrigine by about 55%; doubling the dose of lamotrigine achieved concentrations similar to those with lamotrigine alone.

There is no evidence that **ZESITON** causes clinically significant induction or inhibition of hepatic oxidative medicine-metabolising enzymes. **ZESITON** may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

ZESITON does not seem to affect plasma concentrations of ethinyloestradiol and levonorgestrel following the administration of the oral contraceptive pill. However, any change in the menstrual bleeding pattern should be investigated.

The pharmacokinetics of lithium after 2 g of anhydrous lithium gluconate given twice daily for six days to 20 healthy subjects were not altered by co-administration of 100 mg/day lamotrigine. Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine in 12 subjects and only had a slight increase in the AUC of lamotrigine glucuronide. *In vitro* inhibition experiments indicated that the formation of lamotrigine's primary metabolite, the 2-N-glucuronide, was minimally affected by co-incubation with amitryptyline, bupropion, clonazepam, fluoxetine, haloperidol, or lorazepam. Bufuralol metabolism data from human liver microsome suggested that lamotrigine does not reduce the clearance of medicines eliminated predominantly by CYP2D6. Results of *in vitro* experiments also suggest that clearance of lamotrigine is unlikely to be affected by clozapine, phenelzine, risperidone, sertraline or trazodone.

PREGNANCY AND LACTATION:

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

DOSAGE AND DIRECTIONS FOR USE:

It is important to adhere to the recommended dosages especially in combination therapy with valproate where one-tenth of the normal ZESITON dose is used. Do not exceed the maximum dosage (see **"Warnings and Special Precautions"**).

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

Epilepsy:

DOSAGE IN 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 – 100 mg every 1 – 2 weeks until the optimal response is achieved.

Maintenance dose in monotherapy: The usual 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 **ZESITON** to achieve the desired response.

Adults and Children over 12 years (total daily dose):

Weeks 1 & 2	**Weeks 3 & 4**	**Maintenance Dose**
25 mg (once daily)	50 mg (once daily)	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.

The recommended initial dose and subsequent dose escalation should not be exceeded to minimise the risk of skin rash (see **"Warnings and Special Precautions"**).

DOSAGE IN ADD-ON THERAPY:

Adults and children over 12 years of age:

With enzyme-inducing anticonvulsants only: The initial dose is 50 mg once a day for two weeks, then 100 mg a day, divided into two doses, for two weeks. The dosage may be increased 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.

With enzyme-inducing anticonvulsants and valproic acid: The initial dose is 25 mg once every other day for two weeks, then 25 mg once a day for two weeks. The dosage may be increased by a maximum of 25 – 50 mg a day every 1 or 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 patients taking antiepileptic medicines where the pharmacokinetic interaction with **ZESITON** is currently not known, the dose escalation as recommended for **ZESITON** with concurrent valproate should be used. Thereafter, the dose should be increased until the optimal response is achieved.

Adults and Children over 12 years (total daily dose):

	Weeks 1 & 2	**Weeks 3 & 4**	**Maintenance Dose**
Patients not taking sodium valproate	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.
Patients taking sodium valproate	25 mg (on alternative 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.

The recommended initial dose and subsequent dose escalation should not be exceeded to minimise the risk of skin rash (see "**Warning and Special Precautions"**).

Children aged 2 to 12 years:

The initial **ZESITON** dose in those not taking sodium valproate is 0, 6 mg/kg body mass/day given in two divided doses for two weeks, followed by 1, 2 mg/kg/day 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, the initial **ZESITON** dose is 0,15 mg/kg body mass/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- 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 antiepileptic medicines where the pharmacokinetic interaction with **ZESITON** is currently not known, the dose escalation as recommended for **ZESITON** with concurrent valproate should be used. Thereafter, the dose should be increased until the optimal response is achieved.

CHILDREN AGED 2 TO 12 YEARS (TOTAL DAILY DOSE)

	Weeks 1 & 2	**Weeks 3 & 4**	**Maintenance Dose**
Patients not taking sodium valproate	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 (two divided doses) to a maximum of 400 mg/day.

Patients taking sodium valproate	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.

The recommended initial dose and subsequent dose escalation should not be exceeded to minimise the risk of skin rash (see **"Warnings and Special Precautions"**).

Note: If the calculated daily dose is <5 mg then **ZESITON** should not be administered.

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 **ZESITON** 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"**).

Lamotrigine 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 **ZESITON** to a maintenance stabilisation dose over six weeks (see table below) after which other psychotropic and/or antiepileptic medicines can be withdrawn, if clinically indicated.

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

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

Treatment Regimen	**Week 1 and 2**	**Week 3 and 4**	**Week 5**	**Target Stabilisation Dose (Week 6)**
a. Adjunct therapy with enzyme inhibitors e.g. valproate	12,5 mg (given 25 mg alternate days)	25 mg (once a day)	50 mg (once a day or two divided doses)	100 mg (once a day or two divided doses) (maximum daily dose of 200 mg)
b. Adjunct therapy with enzyme inducers e.g. carbamazepine and phenobarbitone in patients NOT taking valproate	50 mg (once a day)	100 mg (two divided doses)	200 mg (two divided doses)	300 mg in week 6, increasing to 400 mg/day if necessary in week 7 (two divided doses)
c. Adjunct therapy to medicines with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion, OR monotherapy with lamotrigine	25 mg (once a day)	50 mg (once a day or two divided doses)	100 mg (once a day or two divided doses)	200 mg (range 100 – 400 mg) (once a day or two divided doses)
NOTE: In patients taking antiepileptic drugs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine 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 medicines concomitantly such as valproate, the initial **ZESITON** dose is 25 mg every alternate day for two weeks, followed by 25 mg once a day for two weeks. The dose should be increased to 50 mg once a day (or in two divided doses) in week 5. The usual target dose to achieve optimal response is 100 mg/day given once a day or in two divided doses. However, the dose can be increased to a maximum daily dose of 200 mg, depending on clinical response.

b) Adjunct therapy with 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 dose is 50 mg once a day for two weeks, followed by 100 mg/day given in two divided doses for two weeks. The dose should be increased to 200 mg/day given as two divided doses in week 5. The dose may be increased in week 6 to 300 mg/day however, the usual target dose to achieve optimal response is 400 mg/day given in two divided doses, which may be given from week 7.

c) Adjunct therapy to medicines with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion, or monotherapy with lamotrigine:

The initial lamotrigine dose in patients taking concomitant medicines with no known/theoretical pharmacokinetic interaction with lamotrigine, or in monotherapy, is 25 mg once a day for two weeks, followed by 50 mg once a day (or in two divided doses) for two weeks. The dose should be increased to 100 mg/day in week 5. The usual target dose to achieve optimal response is 200 mg/day given once a day as two divided doses. A range of 100 – 400 mg has been used in clinical trials.

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

Maintenance stabilisation total daily dose in BIPOLAR DISORDER following withdrawal of concomitant psychotropic or antiepileptic medicines:

Treatment Regimen	**Week 1**	**Week 2**	**Week 3 onwards**

<table>
<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 original dose</td><td>400 mg</td><td>300 mg</td><td>200 mg</td></tr>
<tr><td>300 mg</td><td>225 mg</td><td>150 mg</td></tr>
<tr><td>200 mg</td><td>150 mg</td><td>100 mg</td></tr>
<tr><td>c. Following withdrawal of other psychotropic or AED medicines with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion</td><td colspan="3">Maintain target dose achieved in dose escalation (200 mg/day) (two divided doses) (range 100 – 400 mg)</td></tr>
<tr><td colspan="4">NOTE: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate should be used.</td></tr>
<tr><td colspan="4">Dose may be increased to 400 mg/day as needed.</td></tr>
</table>

(a) Following withdrawal of adjunct therapy with enzyme inhibitors e.g. valproate:

The dose of **ZESITON** 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 **ZESITON** should be gradually reduced over 3 weeks as the enzyme inducer is withdrawn.

(c) Following withdrawal of adjunct therapy with other psychotropic or antiepileptic 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 **ZESITON** daily dosing in patients with BIPOLAR DISPORDER following addition of other medicines:

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

Adjustment of lamotrigine daily dosing in patients with BIPOLAR DISORDER following the addition of other medicines:

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 lamotrigine	200 mg	100 mg	Maintain this dose (100 mg/day)	
	300 mg	150 mg	Maintain this dose (150 mg/day)	
	400 mg	200 mg	Maintain this dose (200 mg/day)	
b. Addition of enzyme inducers e.g. carbamazepine in patients NOT taking valproate and depending on original dose of lamotrigine	200 mg	200 mg	300 mg	400 mg
	150 mg	150 mg	225 mg	300 mg

	100 mg	100 mg	150 mg	200 mg
c. Addition of other psychotropic or AED 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 AEDs where the pharmacokinetic interaction with **ZESITON** is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate should be used.				

Discontinuation of **ZESITON** in patients with bipolar disorder: Patients may terminate **ZESITON** without a step-wise reduction of dose.

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

GENERAL DOSING RECOMMENDATIONS:

Administration: **ZESITON** (dispersible) should be dispersed in a small volume of water (at least enough to cover the whole tablet). The tablets may also be chewed, or swallowed whole with a little water, if preferred.

SIDE-EFFECTS:

Side Effects:

Blood and the lymphatic system disorders

Less frequent:

Blood dyscrasias including anaemia, eosinophilia, leukopenia or thrombocytopenia

Immune system disorders

Less frequent:

Hypersensitivity syndrome, angioedema

Symptoms such as fever, malaise, influenza-like symptoms, drowsiness, lymphadenopathy, facial oedema, and less frequently, hepatic dysfunction, leukopenia and thrombocytopenia, disseminated intravascular coagulation, multi-organ failure have been reported in conjunction with rashes as part of a hypersensitivity syndrome (see **"Warning and Special Precautions"**).

Psychiatric disorders

Less frequent:

Aggression, hallucinations

Nervous system disorders

Frequent:

Headache, dizziness, drowsiness, coordination abnormalities, ataxia, vertigo, paraesthesia

Less frequent:

Anxiety, confusion, depression, irritability, increased seizures, nystagmus and insomnia, tremor, unsteadiness, movement disorders, worsening of disease, extrapyramidal effects, choreosthetosis

Eye disorders

Frequent:

Vision abnormalities, including blurred vision; and diplopia

Less Frequent:

Conjunctivitis

Gastrointestinal disorders

Frequent:

Nausea and vomiting

Hepatobiliary disorders:

Less frequent:

Increased liver function tests, hepatic dysfunction, hepatic failure

Skin and subcutaneous tissue disorders

Frequent:

Skin rash

Less frequent:

Stevens-Johnson Syndrome, or toxic epidermal necrolysis

The following side-effect has been reported and frequency is unknown:

Photosensitivity

Severe skin rashes, including Stevens-Johnson Syndrome have been reported, especially in children. The skin rash usually occurs within 8 weeks of starting **ZESITON** and resolves on withdrawal of **ZESITON**.

Musculoskeletal, connective tissue and bone disorders

Frequent:

Arthralgia

Less frequent:

Lupus-like reaction

General disorders and administrative site conditions

Frequent:

Pain, back pain, tiredness

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms and signs

Sedation, ataxia, diplopia, nausea and vomiting have been reported.

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.

IDENTIFICATION:

ZESITON 5 mg: White to off–white capsule shaped uncoated tablets debossed with 'H' on one side and '81' on the other side.

ZESITON 25 mg: White to off–white, rounded square shaped uncoated tablets debossed with 'H' on multifaceted side and '80' on flat side.

ZESITON 50 mg: White to off–white, rounded square shaped uncoated tablets debossed with 'H' on multifaceted side and '79' on flat side.

ZESITON 100 mg: White to off–white, rounded square shaped uncoated tablets debossed with 'H' on multifaceted side and '78' on flat side.

ZESITON 200 mg: White to off–white, rounded square shaped uncoated tablets debossed with 'H' on multifaceted side and '77' on flat side.

PRESENTATION:

ZESITON 5 mg TABLETS:

1) Blister Pack:

   Tablets are packed in clear PVC laminated with aclar and printed aluminium foil.

   Each blister contains 10 tablets.

   Pack size: 100's – Each carton contains 10 blisters of 10 tablets each.

2) HDPE Container Pack:

   Tablets are packed in 75 ml white opaque HDPE containers with white opaque polypropylene closures with induction sealing wad, containing cotton coil.

   Each container contains 100 tablets.

Pack size: 100's **-** One HDPE container contains 100 tablets.

ZESITON 25 mg TABLETS:

1) Blister Pack:

Tablets are packed in clear PVC laminated with aclar and printed aluminium foil.

Each blister contains 10 tablets.

Pack size: 60's – Each carton contains 6 blisters of 10 tablets each.

2) HDPE Container Pack:

Tablets are packed in 40 ml white opaque HDPE containers with white opaque polypropylene closures with induction sealing wad, containing cotton coil.

Each container contains 60 tablets.

Pack size: 60's **-** One HDPE container contains 60 tablets.

ZESITON 50 mg TABLETS:

1) Blister Pack:

Tablets are packed in clear PVC laminated with aclar and printed aluminium foil.

Each blister contains 10 tablets.

Pack size: 60's – Each carton contains 6 blisters of 10 tablets each.

2) HDPE Container Pack:

Tablets are packed in 40 ml white opaque HDPE containers with white opaque polypropylene closures with induction sealing wad, containing cotton coil.

Each container contains 60 tablets.

Pack size: 60's **-** One HDPE container contains 60 tablets.

ZESITON 100 mg TABLETS:

1) Blister Pack:

Tablets are packed in clear PVC laminated with aclar and printed aluminium foil. Each blister contains 10 tablets.

Pack size: 60's – Each carton contains 6 blisters of 10 tablets each.

2) HDPE Container Pack:

Tablets are packed in 60 ml white opaque HDPE containers with white opaque polypropylene closures with induction sealing wad, containing cotton coil.

Each container contains 60 tablets.

Pack size: 60's **-** One HDPE container contains 60 tablets

ZESITON 200 mg TABLETS:

1) Blister Pack:

Tablets are packed in clear PVC laminated with aclar and printed aluminium foil.

Each blister contains 10 tablets.

Pack size: 60's – Each carton contains 6 blisters of 10 tablets each.

2) HDPE Container Pack:

Tablets are packed in 120 ml white opaque HDPE containers with white opaque polypropylene closures with induction sealing wad, containing cotton coil.

Each container contains 60 tablets.

Pack size: 60's **-** One HDPE container contains 60 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Keep blisters in the original carton until required for use. Keep the containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

ZESITON 5 mg TABLETS: 45/2.5/0632

ZESITON 25 mg TABLETS: 45/2.5/0633

ZESITON 50 mg TABLETS: 45/2.5/0634

ZESITON 100 mg TABLETS: 45/2.5/0635

ZESITON 200 mg TABLETS: 45/2.5/0636

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

Aurogen South Africa (Pty) Ltd

Woodhill Office Park, Building 1, 53 Phillip Engelbrecht Avenue

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South Africa

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