United Pharmaceuticals

Seizet®

Lamotrigine

Description:
SEIZET® (Lamotrigine) is a use-dependent blocker of voltage gated sodium channels. It produces a use- and voltage dependent block of sustained repetitive firing in cultured neurones and inhibits pathological release of glutamate (the amino acid which plays key role in the generation of epileptic seizures) as well inhibiting glutamate evoked bursts of action potentials.
Properties:
Absorption: Lamotrigine is rapidly and completely absorbed from the gut with no significant first pass metabolism.
Distribution: Peak plasma concentrations occur approximately 2.5 hours after oral drug administration. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. Binding to plasma portions is about 55% it is very unlikely that displacement from plasma proteins would result in toxicity. The volume of distribution is 0.92 to 1.22 L/kg.
Metabolism and Elimination: The mean steady state clearance in healthy adults is 39±14 ml/min. Clearances of Lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material urine less than 10% is excreted unchanged in the urine. Only about 2% of drug related material is excreted in feces.
Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 hours.
Indications.
SEIZET® is indicated for:
- **Epilepsy:**
Mono therapy in adults and children over 12 years of age:
- Simple partial seizures.
- Complex partial seizures.
- Secondarily generalized tonic-clonic seizures.
- Primary generalized tonic-clonic seizures.
Mono therapy in children under 12 years of age is not recommended until such time as adequate information is made available in this particular target population.
Add-on therapy in adults and children over 2 years of age:
- Simple partial seizures.
- Complex partial seizures.
- Secondarily generalized tonic-clonic seizures.
- Primary generalized tonic-clonic seizures.
SEIZET® is also indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome.
Dosage and administration:
SEIZET® Tablets may be chewed, dispersed in a small volume of water (at least enough to cover the whole tablet) or swallowed whole with a little water.
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 SEIZET® (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.
- **Epilepsy:**
When concomitant antiepileptic drugs are withdrawn to achieve SEIZET® mono therapy or other antiepileptic drugs (AEDs) are added on to treatment regimes containing SEIZET® consideration should be given to the effect this may have on Lamotrigine pharmacokinetics.
Restarting Therapy:
Prescribers should assess the need for escalation to maintenance dose when restarting SEIZET® in patient who has discontinued Lamotrigine for any reason, since the risk of serious rash associated with high initial doses and exceeding the recommended dose escalation for Lamotrigine. 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 discounting Lamotrigine exceeds five half-lives; Lamotrigine should generally be escalated to the maintenance dose according to the appropriate schedule as though initiating therapy.
Dosage in mono therapy:
- Adults and children over 12 years (see table 1):
The initial SEIZET® dose in mono therapy is 25 mg once a day for two weeks followed by 50 mg once a day for two weeks thereafter the dose should be increased by a maximum of 50 mg -100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 -200 mg per day given once a day or as two divided doses. Some patients have required 500 mg per day of SEIZET® to achieve the desired response.
The initial dose and subsequent dose escalation should not be exceeded to minimize the risk of rash.
- Children aged 2 to 12 years:
There is insufficient evidence available in children, upon which to base dosage recommendations for monotherapy use in children under the age of 12 years.
Dosage in add – on therapy:
- Adults and children over 12 years (see table 1):
In patient taking Valproate with/without any other antiepileptic drug (AED) the initial SEIZET® dose is 25 mg every alternate day for two weeks followed by 25 mg once a day for two weeks . Thereafter, the dose should be increased by a maximum of 25-50 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200 mg per day given once a day or in two divided doses.
In those patients taking enzyme inducing AEDs with-without other AEDs (except Valproate), the initial SEIZET® dose is 50 mg once a day for two weeks, followed by 100 mg - day given in two divided doses for two weeks. Thereafter the dose should be increased by a maximum of 100 mg every 1-2 weeks until the optimal response is achieved the usual maintenance dose to achieve optimal response is 200-400 mg per day given in two divided doses. Some patient have required 700 mg per day of SEIZET® to achieve the desired response in patient taking AEDs where the pharmacokinetic interaction with Lamotrigine is currently not knows, the dose escalation as recommended for Lamotrigine with concurrent Valproate should be used, thereafter the dose should be increased until optimal response is achieved.

Treatment regimen	Weeks 1+2	Weeks 3+4	Usual Maintenance Dose
Mono therapy	25 mg once a day	50 mg once a day	100-200 mg; Once a day or two divided doses. To achieve maintenance level, doses may be increased by 50-100 mg every one to two weeks.
Add-on therapy with Valproate regardless of any concomitant medications	12.5mg Given 25mg on alternate days	25 mg Once a day	100-200 mg; Once a day or two divided doses. To achieve maintenance level, doses may be increased by 25-50 mg every one to two weeks.
Add-on therapy without Valproate. This dosage regimen should be used with: henytion, Carbamazepine, Phenobarbital, Primidone, or with other inducers of Lamotrigine glucuration	50 mg Once a day	100 mg Two divided doses	200-400 mg two divided doses to achieve maintenance level, doses may be increased by 100 mg every one to two weeks
Note: in patients taking AEDs where the pharmacokinetic interaction with Lamotrigine is currently not know (see interaction with other medicament and other forms of interaction), the treatment regimen as recommended for Lamotrigine with concurrent Valproate should be used, thereafter the dose should be increased until optimal response is achieved.			

The initial dose and subsequent dose escalation should not be exceeded to minimize the risk of rash.
- Children aged 2 to 12 years:
In patient taking Valproate with/without any other anti-epileptic drug (AEDs), the initial SEIZET® dose is 0.15 mg \kg\day given once a day for two weeks, followed by 0.3 mg/kg day given once a day for two weeks. There after 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 in those patients taking enzyme inducing AEDs with/without other AEDs (except Valproate), the initial SEIZET® dose is 0.6 mg/kg/day given in two divided doses for two weeks, followed by 1.2 mg/kg/day for two weeks there after 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 of SEIZET® to achieve optimal response is 5-15mg/kg/day given in two divided doses.
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; there after the dose should be increased until optimal response is achieved.
Table 2 Recommended treatment regimen of SEIZET® for children aged 2-12 year on combined drug therapy (Total daily dose in mg/kg body weight/day).

Treatment regimen	Weeks 1+2	Weeks 3+4	Usual Maintenance Dose
Add-on therapy with Valproate regardless of any other concomitant medication	0.15mg-kg once a day	0.3mg-kg once a day	0.3 mg–kg increments every one to two weeks to achieve a maintenance dose of 1-5 mg –kg once a day or two divided doses.
Add-on therapy without Valproate This dosage regimen should be used with: Phenytion, Carbamazebital, Phenobarbital, Primidone, Or with other inducers of Lamotrigine glucuration.	0.6mg-kg Two divided doses	1.2mg-kg two divided doses	
Note: in patients taking AEDs where the pharmacokinetic interaction with Lamotrigine is currently not known the treatment regimen as recommended Lamotrigine with concurrent Valproate should be used there after the dose should be increased until optimal response is achieved.			
If the calculated daily dose in patient taking Valproate is 1to 2mg then 2mg Lamotrigine may be taken on alternate days for the first two weeks. if the calculated daily dose in patients taking Valproate is less than 1mg then Lamotrigine should not be administered.			

The initial dose and subsequent dose escalation should not be exceeded to minimize the risk of rash. It is likely that patients aged 2-6 years will require a maintenance dose at the higher end of the recommended range.
Children aged less than 2 years: There is insufficient information on the use of SEIZET® in children aged less than 2 years.
Women and hormonal contraceptive:
a) Starting Lamotrigine in patients taking hormonal contraceptive: Dose escalation should follow the guidelines recommended in table above.
b) Starting hormonal contraceptive in patients taking Lamotrigine:
- For women not taking inducers of Lamotrigine glucuronidation such as phenytoin, Carbamazepine, Phenobarbital, Primidone or rifampicin, the maintenance dose of Lamotrigine may need to be increased by as much as two - folds, according to clinical response.
- For women taking Lamotrigine in addition to inducer of Lamotrigine glucuronidation adjustment may not be necessary.
c) Stopping hormonal contraceptives in patients taking Lamotrigine:
- For women not inducers of Lamotrigine glucuronidation the maintenance dose of Lamotrigine may need to be decreased by as much as 50% according to clinical response.
- For women taking Lamotrigine in addition to inducer of Lamotrigine glucuronidation a djustment may not be necessary.
Pregnancy and post-partum: Dose adjustment may be necessary during Pregnancy and post-partum
Elderly: No dosage adjustment from recommended schedule is required. The pharmacokinetics of Lamotrigine in this age group do not differ significantly from a non-elderly population
Hepatic impairment: Initial escalation and maintenance doses should generally be reduced by approximately 50%.
In patient 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.
Contraindications:
Lamotrigine is contraindicated in individuals with known hypersensitivity to Lamotrigine.
Precautions:
Skin rash: There have been reported of adverse skin reactions which have generally occurred within the first 8 weeks after initiation of Lamotrigine treatment, the majority of rashes are mild and self limiting however rarely, serious potentially life threatening skin rashes including Stevens-Johnson Syndromes (SJS) and toxic epidermal necrolysis (TEN) have been reported.
The approximate incidence of serious skin rashes reported as SJS in adults and children over the age of 12 is 1 in 1000 the risk in children under the age of 12 is higher than in adults. Available data from a number of studies suggest that the incidence of rashes associated with hospitalization in children under the age of 12 is from 1 in 300 to 1 in 100.
In children, the initial presentation of rash can be mistaken for an infection; physicians should consider the possibility of a drug reaction in children that develop symptoms of rash and fever during the first eight weeks of therapy.
Additionally the overall risk of rash appears to be strongly associated with:
- High initial doses of Lamotrigine and exceeding the recommended dose escalation of Lamotrigine therapy.
- Concomitant use of Valproate.
- Caution is also required when treating patients with a history of allergy or rash to other antiepileptic drug 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
All patients (adults and children) who develop a rash should be promptly evaluated and Lamotrigine withdrawn immediately unless the rash is clearly not drug related. Lamotrigine should not be restarted in patients with previous hypersensitivity
Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy facial edema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may rarely , lead to disseminated intravascular coagulation (DIC) and multiorgan failure it is important to note that early manifestations of hypersensitivity (e.g. fever, lymphadenopthy) may be present even though rash is not evident.
Patients should be warned to seek immediate medical advice if signs and symptoms develop. If such signs and symptoms are present the patient should be evaluated immediately and Lamotrigine discontinued if an alternative etiology cannot be established.
Epilepsy:
As with other AEDs, abrupt withdrawal of Lamotrigine may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of Lamotrigine should be gradually decreased over a period of 2 weeks during clinical experience with Lamotrigine used as add on therapy, there have been, rarely, deaths following rapidly progressive illnesses with status epilepticus, rhabdomyolysis.
Multi organ dysfunction and disseminated intravascular coagulation (DIC); the contribution of Lamotrigine to these events remains to be established.
Effects on ability to drive and use Machines: An individual variation in response to all antiepileptic drug therapy patients should consult their physician on the specific issues of driving and epilepsy.
Use during pregnancy and lactation:
Pregnancy: No evidence for a substantial increase in the overall risk of major birth malformations associated with Lamotrigine use; one registry has reported an increase in the risk of isolated oral cleft malformations. This increase risk has not been confirmed in a pooled analysis of the data from six other registries. The data on use of Lamotrigine in poly therapy combinations are insufficient to assess whether the risk of malformation associated with other agents is affected by concomitant use, Lamotrigine use as with other medicines Lamotrigine should only be used during pregnancy if the expected benefits outweigh the potential risks.
Lactation: Lamotrigine passes into breast milk in concentrations. The potential benefits of breast feeding should be weighed against the potential risk of adverse effects occurring in the infant.
Drug interactions:
Hormonal Contraceptives: Specialist contraceptive advice should be given to women who are of child bearing age should be encouraged to use effective alternative non-hormonal method of contraception.
- Effects of hormonal contraceptives on Lamotrigine efficacy: Systemic Lamotrigine concentrations are approximately halved during co-administration of oral contraceptive. This may result in reduced seizure control in women on a stable Lamotrigine dose who start an oral contraceptive, or in adverse effects following withdrawal of an oral contraceptive. Dose adjustment of Lamotrigine may be required.
The effects of co-administration of other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect Lamotrigine pharmacokinetic parameters.
- Effects of Lamotrigine on hormonal contraceptive efficacy: An interaction study demonstrated some loss of suppression of the hypothalamic-pituitary-ovarian axis when 300mg Lamotrigine was co-administered with a combined oral contraceptive the impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of decreased contraceptive efficacy cannot be excluded therefore women should have a review of their contraception when starting Lamotrigine and the use of alternative non- hormonal methods of contraception should be encouraged. A hormonal contraceptive should only be used as the sole method of contraception if there is no other alternative. If the oral contraceptive pill is chosen as the sole method of contraception women should be advised to promptly notify their physician if it hey experience changes in menstrual pattern e.g. Breakthrough bleeding) while taking Lamotrigine as this may be an indication of decreased contraceptive efficacy. Women taking Lamotrigine should notify their physician if they plan to start to stop use of oral contraceptive or change to hormonal preparations.
Patient taking other preparations containing Lamotrigine: Lamotrigine should not be administered to patient currently being treated with any other preparation containing Lamotrigine without consulting a doctor.
Dihdrfolate reductase:
SEIZET® is a weak inhibitor of dihydrofiate reductase hence there is a possibility of interference with folate metabolism during long term therapy. However during prolonged human dosing, Lamotrigine did not induced significant changes in the hemoglobine concentration mean corpuscular volume or serum or red blood cell folate concentrations up to 1 year or red blood cell folate concentration for up to 5 years.
Renal failure: In single dose studies in subject s with end stage renal failure plasma concentrations of Lamotrigine were not significantly altered. However accumulation of the glucuronide metabolite is to be expected, caution should therefore be exercised in treating patients with renal failure.
Hepatic impairment: In patients with several hepatic impairment (child-Pugh grade C), it has been shown that initial and maintenance dose should be reduced by 75% caution should be exercised when dosing this severely hepatically impaired population.
Interaction with other medicaments and other forms of interaction:
UDP 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-metabolizing enzymes and interactions between Lamotrigine and drug metabolized 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
Drug that significantly inhibit glucuronidation of Lamotrigine: Valproate.
Drugs that significantly induce glucuration of Lamotrigine: Carbamazepine, Phenytion, Primidone, Phenobarbital, Rifampicin, Ethinylestradiol-levonorgestrel combination
Other hormonal contraceptives and hormone replacement therapy have not been studied they may similarly affect Lamotrigine pharmacokinetic parameters.
Antiepileptic agents which induce drug metabolizing enzymes (such as Phenytion, Carbamazepine, Phenobarbital and Primidone) enhance the metabolism of Lamotrigine and may increased dose requirements
Sodium Valproate which competes with Lamotrigine for hepatic drug-metabolizing enzymes reduces the metabolism of Lamotrigine nearly two fold.
Although changes in the plasma concentrations of other antiepileptic drugs have been reported controlled studies have shown no evidence that Lamotrigine affects the plasma concentration of concomitant antiepileptic drugs Evidence from in vitro studies indicates that Lamotrigine does not displace other antiepileptic drugs from protein binding sites. There have been reports of central nervous system events including headache, nausea, blurred, vision, dizziness, diplopia and ataxia in patients taking Carbamazepine following the introduction of Lamotrigine. These events usually resolve when the dose of Carbamazepine is reduced.
Interactions involving oral contraceptive:
- Effect of oral contraceptives on Lamotrigine: Systemic Lamotrigine concentrations are approximately halved during co-administration of oral contraceptive this may result in reduced seizure control after the addition of an oral contraceptives or adverse effects following withdrawal of an oral contraceptive. Dose adjustments of Lamotrigine may be required.
In a study of 16 female volunteers 30 mcg ethinylestradiol - 150 mcg levonorgestrel in a combined oral contraceptive pill caused an approximately two – fold increase in Lamotrigine or clearance resulting in an average 52% and 39% reduction in Lamotrigine AUC and Cmax, respectively. Serum Lamotrigine concentration at the end of week gradually increased during the course of the week of inactive medication (e.g. Pill-free week) with pre-dose concentration at the end of the week of inactive medication being on average approximately two fold higher than that during co therapy.
The effect of other hormonal contraceptive products or hormone replacement therapy has not been evaluated although the effect may be similar.
- Effect of Lamotrigine on oral contraceptive: Co-administration of 300mg Lamotrigine in a study of 16 female volunteers had no effect on the pharmacokinetics of the ethinylestradiol component of a combined oral contraceptive pill. A modest increase in oral clearance of the levonorgestrel component was observed, resulting in an average 19% and 12% reduction in levonorgestrel AUC and Cmax respective measurement of serum follicle stimulating hormone (FSH) Luteinising hormone (LH) and estradiol during the study indicated some loss of suppression of ovarian hormonal activity although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance and the changes in serum FSH and LH on ovarian ovulatory activity is unknown. Vaginal bleeding was reported by some volunteers the effects of dose of Lamotrigine volunteers unknown. The effects of dose of Lamotrigine other - day have not been studied than 300mg–days have not been studied and studies with other female hormonal preparations have not been conducted.
Side effects:
In double – blind add on clinical trials skin rashes occurred in up to 10% of patient taking Lamotrigine and 5% of patient taking placebo the skin rashes led to the withdrawal of Lamotrigine treatment in 2% of patients. The rash, usually maculopulare in appearance generally appears within eight weeks of starting treatment and resolves on withdrawal of Lamotrigine.
Rarely serious potentially life threatening skin rashes, including Stevens -Johnson syndrome and toxic epidermal necrolysis (Lyell syndrome) have been reported. Although the majority recover on drug withdrawal, some patients experience irreversible scarring and there have been rare cases of associated death.
The approximate incidence of serious skin rashes reported as SJS in adults and children over the age of 12 in 1000. The risk in children under the age of 12 is higher than in adults.
Available data from a number of studies suggest that the incidence in children under the age of 12 requiring hospitalization due to rash ranges from 1 in 300 to 1in 100.
In children, the initial presentation of a rash can be mistaken for an infection; physicians should consider the possibility of a drug reaction in children that develop symptoms of rash and fever during the first eight weeks of therapy.
- Additionally the overall risk of rash appears to be strongly associated with.
- High initial doses of Lamotrigine and exceeding the recommended dose escalation of Lamotrigine therapy.
-Concomitant use of Valproate.
All patients (adults and children) who develop a rash should be promptly evaluated and Lamotrigine withdrawn immediately unless the rash is clearly not drug related.
Rash has also been reported as part of hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymohadenopathy facial edema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may rarely, lead to disseminated intravascular coagulation (DIC) 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 patients should be warned to seek immediate medical advice if signs and symptoms develop. If such signs and symptoms are present the patient should be evaluated immediately and Lamotrigine discontinued if an alternative etiology cannot be established.
Adverse experience reported during Lamotrigine mono therapy trials includes headache Tiredness, rash, nausea, dizziness, drowsiness and insomnia.
Other adverse experiences have include diplopia, blurred vision conjunctive dizziness, drowsiness, headache, Tiredness, gastrointestinal disturbance (including vomiting and diarrhea) irritability-aggression, tremor, agitation, confusion and hallucination. Very rarely, lupus-like reactions have been reported
There have been reports of hematological, abnormalities which may or may not be associated with the hypersensitivity syndrome. These have included neutropenia, leucopenia anemia, thrombocytopenia, pancytopenia and very rarely a plastic anemia and agranulocytosis.
Movements disorder such as tics unsteadiness, ataxia, nystagums and tremor have also been reported. There have been reports that Lamotrigine may worsen parkinsonian symptom patients with pre-existing Parkinson's disease and isolated reports of extrapyramidal effects and choreoathetosis in patient with this underlying condition very rarely, increase in seizure frequency has been reported.
Elevations of liver function tests and rare report s of hepatic dysfunction, including hepatic failure, have been reported. Hepatic dysfunction usually occurs in association with hypersensitivity reactions but isolated cases have been reported without overt signs of hypersensitivity.
Overdosage:
Symptoms and signs: Acute ingestion of doses in excess of 10-20 times the maximum therapeutic dose has been reported. Over dose has resulted in symptoms including nystagmus, ataxia, impaired consciousness and coma.
Treatment: In the event of over dosage, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage should be performed if indicated.
Storage conditions:
Store up to 30°C.
Presentation:
SEIZET® 25: Each dispersible/chewable tablet contains Lamotrigine 25mg in packs of 30 tablets.
SEIZET® 100: Each dispersible/chewable tablet contains Lamotrigine 100mg in packs of 30 tablets.
Hospital packs are also available.
Excipients:
Calcium Carbonate, Povidone, Sodium Starch Glycolate, Aluminum Magnesium Silicate, Sodium saccharine, Low-substituted hydroxypropyl cellulose, Black current flavor and Magnesium stearate.

This is a medicament

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep medicament out of the reach of children.

COUNCIL OF ARAB HEALTH MINISTERS
UNION OF ARAB PHARMACISTS

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